Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for new claims 44-57 may be found in the specification at pages 8-17, at pages 18-19, at pages 25-26, and throughout the Examples and the drawings; and support for the amendments to claim 16 may be found in the specification at page 8, line 14 to page 9, line 2, and in Example 1 at pages 45-46. Hence, the foregoing amendments to the claims do not add new matter, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, new claims 44-57 are sought to be entered, and claim 16 has been amended. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 14-20, 27 and 32-57 are pending in the application, with claims 14, 16 and 44 being the independent claims.

III. Summary of the Office Action

In the Office Action dated April 11, 2002, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks to accommodate or traverse each of these elements of the Office Action.

IV. The Rejection Under 35 U.S.C. § 112 Second Paragraph

In the Office Action at page 2, sections 2-3, the Examiner has rejected claims 16-20, 27, 31 and 33-43 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. By the foregoing amendments, claim 31 has been cancelled without prejudice or disclaimer, and for reasons unrelated to patentability and unrelated to the present rejection. Hence, the portion of this rejection that may have applied to claim 31 has been rendered moot. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

In making this rejection, the Examiner contends that claim 16 (and thus the claims depending therefrom) is indefinite for reciting "one or more integration sequences, each comprising at least one recombination site . . . ." Specifically, the Examiner contends that the recitation of "each" in claim 16 suggests the use of more than one integration sequence. Applicants note that claim 16 recites the use of "*one or more* integration sequences," thereby encompassing situations in which one integration sequence is used, *and* those in which more than one integration sequence is used. Solely for the purposes of clarification, and without narrowing its scope, claim 16 has been amended to replace "each" with "said one or more integration sequences."

Thus, it is believed that this rejection has been fully accommodated. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

V. The Rejection of Claims 14-20, 27, 32 and 33 Under 35 U.S.C. § 102(b) Over Stemmer Is Traversed

The Examiner has first rejected claims 14-20, 27, 32 and 33 for allegedly being anticipated by Stemmer (U.S. Patent No. 5,605,793; Doc. AB3, of record; hereinafter "Stemmer"). *See* Office Action at pages 3-5, section 5. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Stemmer teaches method for *in vitro* recombination which can be used in many different genes encoded proteins [sic]. One aspect of this invention provided a method for introducing one or more mutations into a template double-stranded polynucleotide, wherein the template *double-stranded polynucleotide had been cleaved into random fragments of a desired size,* by adding to the resultant population of double-stranded fragments one or more single or double-stranded oligonucleotides, wherein said oligonucleotides comprised an area of identity and an area of heterology to the template polynucleotide; *denaturing the resultant mixture of double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which resulted in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide*; and repeating the above steps as desired.

Office Action at pages 3-4, section 5, line 2, to line 9 (emphasis added). Applicants respectfully disagree with these contentions.

Contrary to the Examiner's above-noted contentions, Stemmer does not disclose all of the elements of independent claims 14 and 16 (and thus of the remaining claims that ultimately depend therefrom). In particular, Stemmer does not disclose an operative method for the insertion of one or more integration sequences into a nucleic acid molecule in the presence of one or more recombination proteins. Instead, Stemmer only discloses a method for performing a non-specific and non-targeted (random) sequence exchange which requires

the initial restriction enzyme cleavage of the insert and target molecules, followed by a temperature-dependent homologous recombination via traditional crossing-over. *See* Stemmer at col. 3 line 4, line 19; in Example 1 at col 11, line 40, to line 42 (DNAse I digestion of the DNA substrate); in Example 2 at col 13, line 21, to line 23; in Example 3 at col 14, line 29, to line 30; and in Figure 2. As one of ordinary skill would readily understand, the insertion methods recited in the present claims, in which recombination proteins are involved, do not involve the initial digestion and subsequent ligation of the substrates as disclosed by Stemmer. In fact, Stemmer contains no disclosure of the use of recombination proteins as recited in the present claims.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As noted above, Stemmer does not expressly or inherently disclose the presently claimed methods. Hence, under *Kalman*, this reference cannot and does not anticipate the claims as currently presented.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection of claims 14-20, 27, 32 and 33 under 35 U.S.C. § 102(b) over Stemmer are respectfully requested.

VI. The Rejection of Claims 16-20, 27, 32 and 33 Under 35 U.S.C. § 102(b) Over Atlung Is Traversed

The Examiner has next rejected claims 16-20, 27, 32 and 33 for allegedly being anticipated by Atlung (*Gene 107*: 11-17 (October 1991); Doc. AT4, of record; hereinafter

"Atlung"). *See* Office Action at pages 5-7, section 6. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner repeats the contentions made in the previous Office Action (Paper No. 8):

> ligation sites (restriction sites) could be considered as "recombination sites" since "recombination site" was defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see specification, page 23, last paragraph) and ligase could be considered as a recombination protein.

Office Action at page 7, lines 4-8. Applicants respectfully disagree with these contentions.

Contrary to the Examiner's above-noted contentions, ligation sites (restriction sites) would not be considered as "recombination sites" by one of ordinary skill as those terms are used in the present application. As noted above, the presently claimed methods in which recombination proteins are involved are distinct from traditional restriction/ligation cloning. In addition, the recombination proteins that are involved in the methods of the present invention are distinct from ligases. Therefore, as was the case for Stemmer, the traditional restriction/ligation methods disclosed in Atlung are not the same as the methods of the present invention.

In view of the foregoing remarks and under *Kalman*, Applicants respectfully assert that Atlung cannot and does not anticipate the claims as currently presented. Reconsideration and withdrawal of the rejection of claims 16-20, 27, 32 and 33 under 35 U.S.C. § 102(b) over Atlung therefore are respectfully requested.

VII. The Rejection of Claims 14-20, 27 and 30-43 Under 35 U.S.C. § 102(a) or § 102(e) Over Hartley Is Traversed

In the Office Action at pages 7-8, section 7, the Examiner has rejected claims 14-20, 27 and 30-43 under 35 U.S.C. § 102(a) or § 102(e) as being anticipated by Hartley (U.S. Patent No. 5,888,732: Doc. AF3, of record; hereinafter "Hartley"). By the foregoing amendments, claims 30 and 31 have been cancelled without prejudice or disclaimer, and for reasons unrelated to patentability and unrelated to the present rejection. Hence, the portion of this rejection that may have applied to claims 30 and 31 has been rendered moot. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

Independent claims 14 and 16 each are drawn to methods comprising, *inter alia*, inserting one or more integration sequences comprising at least one recombination site into at least one nucleic acid molecule. In contrast, Hartley does not disclose the insertion of one or more integration sequences into at least one nucleic acid molecule. As one of ordinary skill would readily appreciate, the term "integration sequence" as used in the present specification refers to specific mobile genetic elements, *i.e.*, nucleic acid molecules or segments with integrative activity, such as transposons, insertion sequences, integrating viruses, homing introns, or other integrating elements, or various combinations thereof. *See, e.g.*, specification at page 34, lines 7-29. Thus, the "nucleic acid sequence having kam marker" depicted in Figure 2A of Hartley, alleged by the Examiner to be considered as an "integration sequence" (*see* Office Action at page 8, lines 15-16), cannot be considered an integration sequence as that term is used in the present specification.

In view of the foregoing remarks and under *Kalman*, Applicants respectfully assert that Hartley cannot and does not anticipate the claims as currently presented. Reconsideration and

withdrawal of the rejection under 35 U.S.C. §§ 102(a) or (e) over Hartley therefore are respectfully requested.

VIII. The Rejection of Claims 14-20, 27 and 30-43 Under 35 U.S.C. § 102(f) Is Traversed

In the Office Action at page 9, section 8, the Examiner has rejected claims 14-20, 27 and 30-43 under 35 U.S.C. § 102(f). By the foregoing amendments, claims 30 and 31 have been cancelled without prejudice or disclaimer, and for reasons unrelated to patentability and unrelated to the present rejection. Hence, the portion of this rejection that may have applied to claims 30 and 31 has been rendered moot. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

As the examiner has noted, the '732 patent (*i.e.*, "Hartley") was assigned by the inventors (who are also inventors in the present application) to Life Technologies, Inc. ("LTI"). The present application has been assigned to Invitrogen Corporation. On September 14, 2000, LTI merged with Invitrogen Corporation, with the surviving company retaining the name Invitrogen Corporation (a copy of the merger document was recorded in the USPTO against Hartley on July 9, 2002). As a result of this merger, Invitrogen Corporation is the current owner of the entire right, title and interest, both of Hartley and of the present application. Accordingly, Invitrogen Corporation, in the form of its predecessor in interest LTI, was the owner of Hartley on the date that the invention claimed in the present application was made. Hence, Applicants respectfully assert that they did, indeed, invent the claimed subject matter.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection of claims 14-20, 27 and 30-43 under 35 U.S.C. § 102(f) therefore are respectfully requested.

IX. The Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting is Traversed

In the Office Action at pages 9-10, the Examiner has rejected claims 14-20, 27 and 30-43 under the judicially created doctrine of obviousness-type double patenting over certain claims in Hartley. By the foregoing amendments, claims 30 and 31 have been cancelled without prejudice or disclaimer, and for reasons unrelated to patentability and unrelated to the present rejection. Hence, the portion of this rejection that may have applied to claims 30 and 31 has been rendered moot. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

For the reasons discussed above distinguishing the presently claimed invention from the disclosure of Hartley, Applicants respectfully disagree with the Examiner's contention that the claims of the present invention are not patentably distinct from claim 29 of Hartley. Applicants therefore respectfully request that this rejection be reconsidered and withdrawn.

X. Conclusion

All of the stated grounds of rejection have been properly traversed or accommodated. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner

believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendment and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

(a) Claims 30 and 31 are cancelled without prejudice or disclaimer.

(b) Pending claims 14 and 16 are sought to be amended as follows:

14. (Once amended) A method of cloning a nucleic acid molecule or a population of nucleic acid molecules comprising:

inserting one or more integration sequences comprising at least one recombination site into at least one nucleic acid molecule; and

transferring one or more nucleic acid molecules [flanked by] comprising recombination sites [by recombinational cloning] into one or more vectors in the presence of one or more recombination proteins.

16. (Twice amended) A method for producing a nucleic acid molecule or a population of nucleic acid molecules comprising:

inserting one or more integration sequences, said one or more integration sequences comprising at least one recombination site, into at least one nucleic acid molecule thereby producing a nucleic acid molecule comprising at least a first and a second recombination site; and

causing said at least first and second recombination sites to recombine [via a recombinational cloning reaction] in the presence of at least one recombination protein.

(c) New claims 44-57 are sought to be entered.

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